American Journal of Medical Genetics 63:193–197 (1996)

Bilateral Radial Deficiency With Lower Limb Involvement

Stephanie Spranger, Michael Weber, Jochen Tröger, Gholamali Tariverdian, and John M. Opitz

Institute of Human Genetics (S.S.,G.T.), Department of Orthopedics (M.W.), Department of Pediatric Radiology (J.T.), University of Heidelberg, Germany; and Foundation for Developmental and Medical Genetics, Helena, Montana (J.M.O.)

We describe a 10-month-old boy with an unclassified form of radial aplasia with absent thumbs, tibia hypo/-aplasia, and partial absence of toes. Only a few cases with similar limb deficiencies have been published. We try to classify the malformations on the basis of embryological considerations and discuss possible differential diagnosis.

KEY WORDS: absent radii, absent thumbs, developmental field defect, homologous field, tibia aplasia, tibia hypoplasia

INTRODUCTION

Radial defects are phenotypically variable and genetically heterogeneous. They occur in autosomal recessive syndromes such as the thrombocytopenia-absent radius syndrome (TAR) [Hall, 1987] or sporadically as in the VACTERL-association [Corsello et al., 1992] and are often associated with malformations of the genitourinary tract and the cardiovascular system [Carroll and Louis, 1974]. They may also be accompanied by malformation of the lower limbs, such as absent tibia, absent fibula, and hypoplastic femur, especially if the upper limb involvement is symmetrical [Evans et al.,1993].

There is evidence that homology of development of upper and lower limbs exists [Opitz, 1993, 1995]. Ulna and fibula, radius, and tibia are corresponding, i.e., homologous structures. This is well documented in mesomelic dysplasia, Reinhardt-Pfeiffer type [Reinhardt and Pfeiffer, 1967] in which fibula and ulna are absent.

Limb morphogenesis occurs primarily during the period of organogenesis, stage 14 (day 28) until stage 23 (day 56) [Lewin and Opitz, 1986]. Development of the limbs first occurs in a proximal-distal direction, where morphogenesis of distal structures depends on the morphogenesis of the proximal. Tibia and radius both are "preaxial" or anterior structures.

Our patient's findings further confirm the homology of the preaxial structures of upper and lower limbs.

CLINICAL REPORT

The patient was the first child of his parents. At the time of birth his mother was 26 and his father 32 years old. As a child the father had torticollis, which improved with physiotherapy. At the time of examination he was healthy, height was 165 cm. One of his sisters has a son with Poland anomaly. The pedigree is in Figure 1.

The mother is healthy and of normal height (160 cm). At examination she has apparent frontal prominence.

Pregnancy was unremarkable. The mother denied medicine or drug exposure. The patient was born at term, birthweight was 2,045 g (−2.7 SD), length was 45 cm (−2.5 SD), and occipitofrontal circumference was 34 cm. At birth, multiple limb malformations were detected. Thumbs were absent, hands were held in 90 degree flexion (clubhand). Elbows and shoulders were unremarkable, movements and muscles were normal. Hips were normal with no limitation of abduction. Both knees were held in flexion (90 and 70 degrees), the legs were short and on the right side he lacked three toes (toes 1, 2, 3). He had cryptorchidism and an inguinal hernia on both sides. Feeding and psychomotor development were normal: he smiled at 6 weeks, turned at 5 months, and sat unsupported at 7 months. He never had an episode of bleeding. Hearing and ophthalmological findings were normal.

On examination at 10 months his length was 64 cm (−3.58 SD) and weight was 6,010 g −3.07 SD). Hands were radially deviated, although the deformities had improved with casting (Fig. 2). Knees were in mild flexion (Fig. 3). External genitalia were normal.

The boy had apparent frontal bossing and a frontal cutaneous hemangioma (Fig. 4). Ultrasound examination showed no internal abnormalities. Cardiac status

Received for publication October 30, 1995; revision received January 10, 1996.

Address reprint requests to Dr. Stephanie Spranger, Institute of Human Genetics and Anthropology, Im Neuenheimer Feld 328, 69120 Heidelberg, Germany.

Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

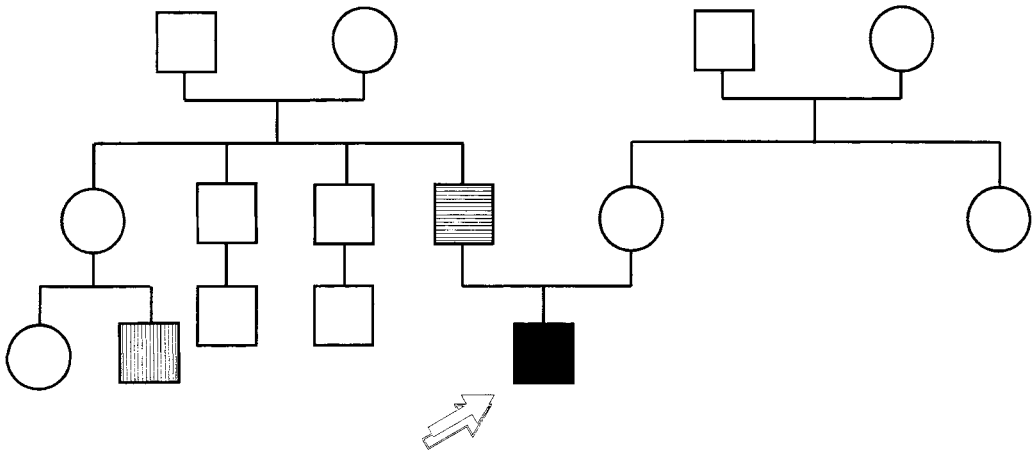

Fig. 1. Pedigree: ■, Patient; ▤, Torticollis as a child; ▥, Poland anomaly.

was normal. Radiological studies at the age of 4 and 12 months showed absence of thumb, metacarpal I and radius on both sides (Fig. 5). Pelvis and femora were normal. Also noted were shortness of the right fibula (Fig. 6); absent right tibia (Fig. 6); hypoplasia of left tibia (Fig. 6a,b); left foot with five digits, digits 2-5 hypoplastic (Fig. 7a); right foot with 3 metatarsals and 2 digits, one digit with only 2 phalanges, one being hypoplastic (Fig. 7b).

Results of laboratory studies showed normal male karyotype (46, XY) and no premature centromere separation. Platelet and erythrocyte numbers were normal. Fanconi anemia was excluded by non-sensitivity to DEB.

Dermatoglyphic studies showed distal and slightly more medial placement of the axial triradii and encroachment of non-ridged skin into the thenar eminence; otherwise unremarkable.

DISCUSSION

The pattern of limb malformation seen in this patient with absent thumbs and radii, as well as tibial-aplasia or -hypoplasia does not fit one of the well-known malformation syndromes with absent radii and/or thumbs such as TAR syndrome, Roberts syndrome or Fanconi anemia.

In the TAR syndrome the radii are absent and severe deficiency of leg long bones is rare [Anayane-Yeboa et al., 1985]. But in contrast to the present case, the thumbs are always present [Hall, 1987]. The presence of thumbs in case of absent radii can be viewed as a valuable piece of evidence in favor of the Shubin-Alberch-Oster hypothesis [Opitz, 1995], according to which the medial curvature of the homologized metapterygial axis makes all digits postaxital structures, and with the only distal radial derivate (the radiale/prepollex) becoming the distal radial styloid process. According to the hypothesis, recently dramatically supported by the work of Sordino et al. [1995; q.v. also the editorial comment of Nelson and Tabin, 1995] it is entirely possible to form thumbs in the absence of radii.

In Roberts syndrome the limb defects usually involve all four limbs, tend to be symmetrical, and are more severe in the upper than in the lower limbs. Radial aplasia and lack of thumbs is frequent [Van den Berg and Francke, 1993]. Prenatal growth deficiency and facial hemangioma also are common findings. But in contrast to patients with Roberts syndrome, the patient presented here neither has mid-facial clefting, abnormalities of the eye nor the chromosome anomalies, which can be demonstrated in 79% of patients with Roberts syndrome [Van den Bergh and Francke, 1993].

Patients with Fanconi anemia mostly have abnormalities of the thumbs while malformations of other bones are rare [Glanz and Fraser, 1982]. Anemia characteristically develops during early childhood; metaphase chromosomes show an increase of chromatid breaks, gaps, and chromosome rearrangement due to alkylating agents [Latt et al, 1982]. These laboratory findings were

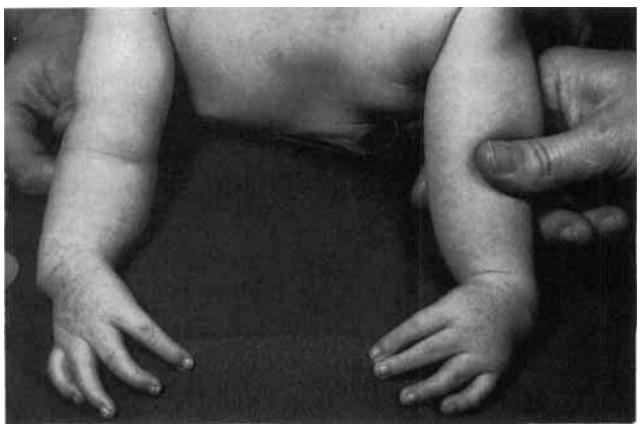

Fig. 2. Patient at 10 months; absent thumbs and clubhand position.

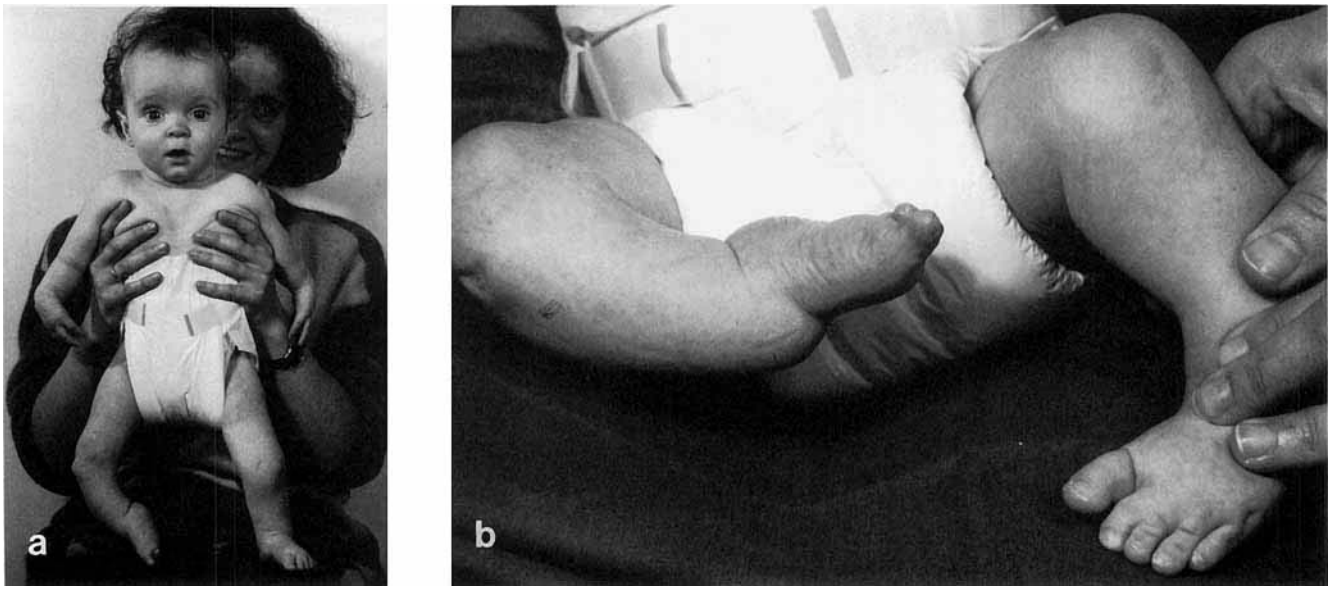

Fig. 3. **a,b:** Patient at 10 months demonstrating severe involvement of lower limbs. Note short legs and foot malformation on the right.

not present in our patient. We are not able to classify the malformation of the patient.

Associated malformations of the lower limb with radius and thumb abnormalities seem to be relatively rare [Czeizel et al., 1993]. Similar previous cases are cited in three sources: Drinnenberg [1935], Birch-Jensen [1949], and Temtamy and McKusick [1978]. Drinnenberg [1935] mentioned a child with absent radius and thumb on the left side and hypoplasia of the right hand. Hip dysplasia, tibial defect on the left, and oligodactyly of the feet were also present. The father of this child had split feet.

Among 78 cases studied by Birch-Jensen [1949] only two sporadic cases with forearm hypoplasia were found

Fig. 4. Patients face at the age of 10 months with frontal bossing and frontal hemangioma. Normal family resemblance.

Fig. 5. Radiographs of upper limbs at the ages of 4 and 12 months.

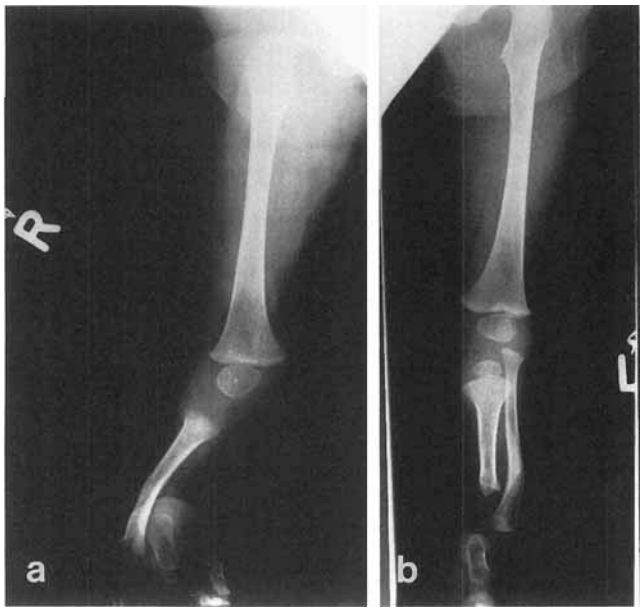

Fig. 6. **a,b:** Radiograph of patient's lower limbs at the age of 4 months.

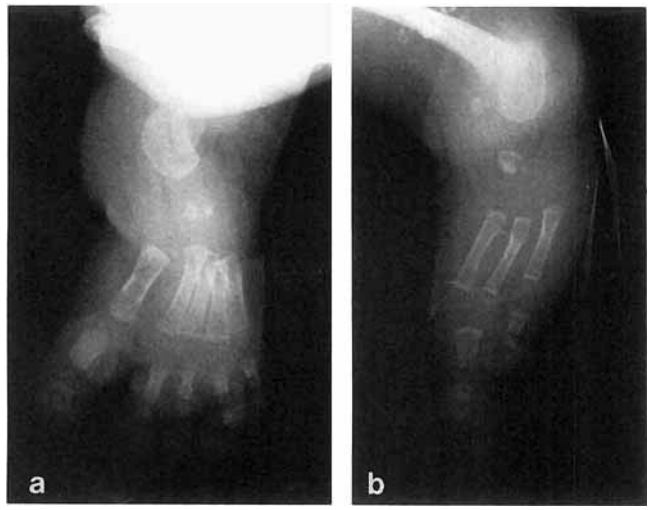

Fig. 7. **a:** Radiograph of patient's left foot at 12 months. **b:** Radiograph of patient's right foot at 12 months.

to have associated anomalies of the lower limbs in the *form of* absent tibia, absent fibula, and hypoplastic femur.

Temtamy and McKusick [1978] described a 3-year-old black girl with absent radii, absent thumbs,and clubhand deformity. She had absence of the tibiae and lateral dislocation of the upper ends of the fibulae and the fibulofemoral joint. She had no other associated skeletal or visceral malformations.

Like the patients described above [Drinnenberg, 1935; Birch-Jensen, 1949; Temtany and McKusick, 1978] our patient has symmetrical involvement of the upper limbs and asymmetrical involvement of the lower limbs, affecting preaxial structures [Siervogel et al., 1979].

Homologous anterior limb involvement may occur in the infants of diabetic mothers. Grix [1982] has documented cases with radial aplasia, tibial duplication with bifid digit, and ankle and other anomalies of blastogenesis.

In our patient teratogenic agents probably are excluded, since there was no drug exposure during pregnancy. However, an extensive developmental field defect [Opitz, 1993, 1995] is probable, affecting radial and tibial structures as part of a homologous field. During blastogenesis the limb arises as a prepatterned single morphogenetic field. The formation of the developing limb bud is initiated by the mesenchyme. As the limb bud grows three major axes appear. Positional information for specifying the anterior-posterior axis is already present in the lateral plate mesenchyme prior to bud formation. The dorso-ventral axis is established later and is defined by the ectoderm. The proximal-distal axis is determined during the growth of the limb bud in the rapidly dividing mesenchymal cells under the apical ectodermal ridge (AER). The AER promotes mesenchymal growth, keeps the mesenchyme undifferentiated, and directly or indirectly provides positional information along the proximal-distal axis. The proximal-distal axis in limb development appears to be induced by the interaction between the apical ectodermal ridge and the underlying mesenchyme in the region termed the progress zone [Tabin, 1991].

Growth and patterning of the tetrapod limb skeleton [Sordino et al.,1995] are initiated by Hox-genes. Five contiguous genes in the 5'region of the Hox-D complex (Hox 9–13) display specific and colinear expression domains in the mesenchyme of the developing limb buds resulting from the successive activation of these genes in the posterior and distal area of the buds.

Whether Hox-gene expression , i.e., the cascade of expression of different Hox-genes, is disturbed in the case presented must remain speculation.

Recent work has contributed much to an understanding of the signaling systems that specify the three limb axes including the FGF4, sonic hedgehog, Wnt-7a, and Lmx1 gene products [Martin, 1995; Parr and McMahon, 1995; Vogel et al., 1995; Yang and Niswander, 1995].

Our case illustrates that in the presence of only a proximal tibia five toes can be formed. This indicates that formation of hallux and 2nd and 3rd toes does not depend on the presence of the distal tibia. However, complete absence of tibia may allow formation of only three metatarsals with two toes.

ACKNOWLEDGMENTS

We are most grateful to Dr. John P. Johnson for expert editing and additional discussion.

REFERENCES

Anayane-Yeboa K, Jaramillo S, Nagel C, Grebin B (1985): Tetraphocomelia in the syndrome of thrombocytopenia with absent radius. Am J Med Genet 20:571–576.

Birch-Jensen A (1949): Congenital Deformities of the Upper Extremities. Kopenhagen: E. Munksgaard.

Carroll RE, Louis DS (1974): Anomalies associated with radial dysplasia. J Pediatr 84:409–411.

Corsello G, Maresi E, Corrao AM, Dimita U, Lo-Cascio M, Cammarata M (1992): VATER/VACTERL association: clinical variability and expanding phenotype including laryngeal stenosis. Am J Med Genet 44:813–815.

Czeizel AE, Vitez M, Kodaj I, Lenz W (1993): A family study on isolated congenital radial and tibial deficiencies in Hungary, 1975–1984. Clin Genet 44:32–36.

Drinnenberg A (1935): Klumphandbildung infolge angeborenen Radiusdefektes und ihre Behandlung. Z Orthop Chir 63:297.

Evans JA, Vitez M, Czeizel A (1993): On the biological nature of associations: Evidence from a study of radial deficiencies and associated malformations. In Opitz JM (ed): "Blastogenesis: Normal and Abnormal." New York: Wiley-Liss for the March of Dimes Birth Defects Foundation: BD:OAS XXIX (1):63–81.

Glanz A, Fraser FC (1982): Spectrum of anomalies in Fanconi anemia. J Med Genet 19:412–416.

Grix A Jr (1982): Invited Editorial Comment: Malformations in infants of diabetic mothers. Am J Med Genet 13:131–137.

Hall JG (1987): Thrombocytopenia and absent radius (TAR) syndrome. J Med Genet 24:79–83.

Latt SA, Kaiser TN, Lojewski A, Dougherty C, Juergens L, Brefach S, Sahar E, Gustashaw K, Schreck RR, Powers M, Lalande M (1982): Cytogenetics and flow cytometric studies of cells from patients with Fanconi's anemia. Cytogenet Cell Genet 33:133–138.

Lewin SO, Opitz JM (1986): Fibular a/hypoplasia: Review and documentation of a fibular developmental field. Am J Med Genet Supp 2: 215–238.

Martin GR (1995): Why thumbs are up. Nature 374:410–411.

Nelson CE, Tabin C (1995): Footnote on limb evolution. Nature 375: 630–631.

Opitz JM (1993): Blastogenesis and the "primary field" in human development. New York: Wiley Liss for the National Foundation—March of Dimes. BD:OAS XXIX (I):3–37.

Opitz JM (1995): Limb anomalies from evolutionary, developmental and genetic perspectives. In Neri G, Martini-Neri E, Opitz JM (eds): " Gene Regulation and Fetal Development." New York: Wiley-Liss, in press.

Parr BA, McMahon AP (1995): Dorsalizing signal Wnt 7a required for normal polarity of D-V and A-P axes of mouse limb. Nature 374: 350–353.

Reinhardt K, Pfeiffer RA (1967): Ulno-fibuläre Dysplasie. Eine autosomal-dominant vererbte Mikromesomelie ähnlich dem Nievergeltsyndrom. Fortschr Roentgenstr 107:379–391.

Siervogel RM, Roche AF, Roche EM (1979): The identification of developmental fields using distributions of fingerprint patterns and ridge counts. New York: Alan R. Liss, Inc., for the National Foundation: March of Dimes. BD:OAS XV (6):135–147.

Sordino P, van der Hoeven F, Duboule D (1995): Hox gene expression in teleost fins and the origin of vertebrate digits. Nature 375: 678–681.

Tabin CJ (1991): Retinoids, homeoboxes, and growth factors: Towards molecular models for limb development. Cell 66:199–217.

Temtamy S, McKusick VA (1978): The genetics of hand malformations. New York: Alan R. Liss, Inc., for the National Foundation—March of Dimes. BD:OAS XIV (3):1–619.

Van den Berg DJ, Francke U (1993): Roberts syndrome: A review of 100 cases and a new rating system for severity. Am J Med Genet 47:1104–1123.

Vogel A, Rodriguez C, Warnken W, Izpisua Belmonte (1995): Dorsal cell specified by chick LmxI during vertebrate limb development. Nature 378:116–120.

Yang Y, Niswander L (1995): Interaction between the signaling molecules Wnt 7a and SHH during vertebrate limb development: Dorsal signals regulate anteriorposterior patterning. Cell 80:939–947.